Armed Forces College of Medicine

AFCM

ROLE OF KIDNEY IN TRANSPORT OF AMINO ACIDS AND METABOLIC DISORDERS AFFECTING KIDNEY

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By the end of this lecture the student will be able to:

1. Describe the role of kidney in amino acid transport.
2. Elaborate the biochemical aspects of Hartnup disease and other Inborn error of renal amino acids transport
3. Interpret the biochemical bases of Cystinuria and Cystinosis
4. Explain the Causes of Hyperoxaluria.

Lectures outlines

- **Mechanisms of amino acids transport in kidney?**

1-Active facilitated transport system

Inborn error of renal amino acids transport

1- Hartnup disease

2- Iminoglycinuria

3- Cystinuria

2- Gamma Glutamyl cycle:-

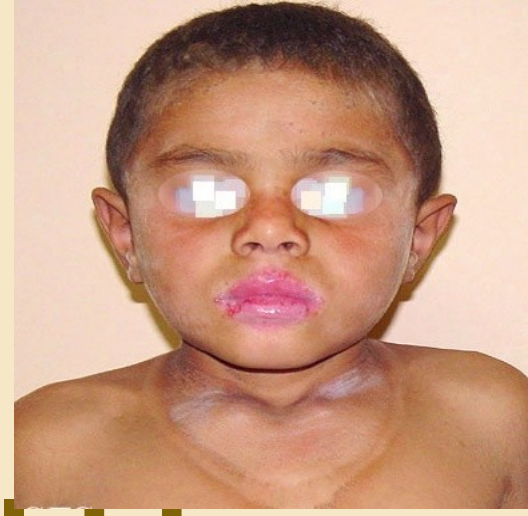
clinical significance of GGT?OXOPROLINUREA

- **Metabolic disorders affecting kidney**

1- Cystinosis

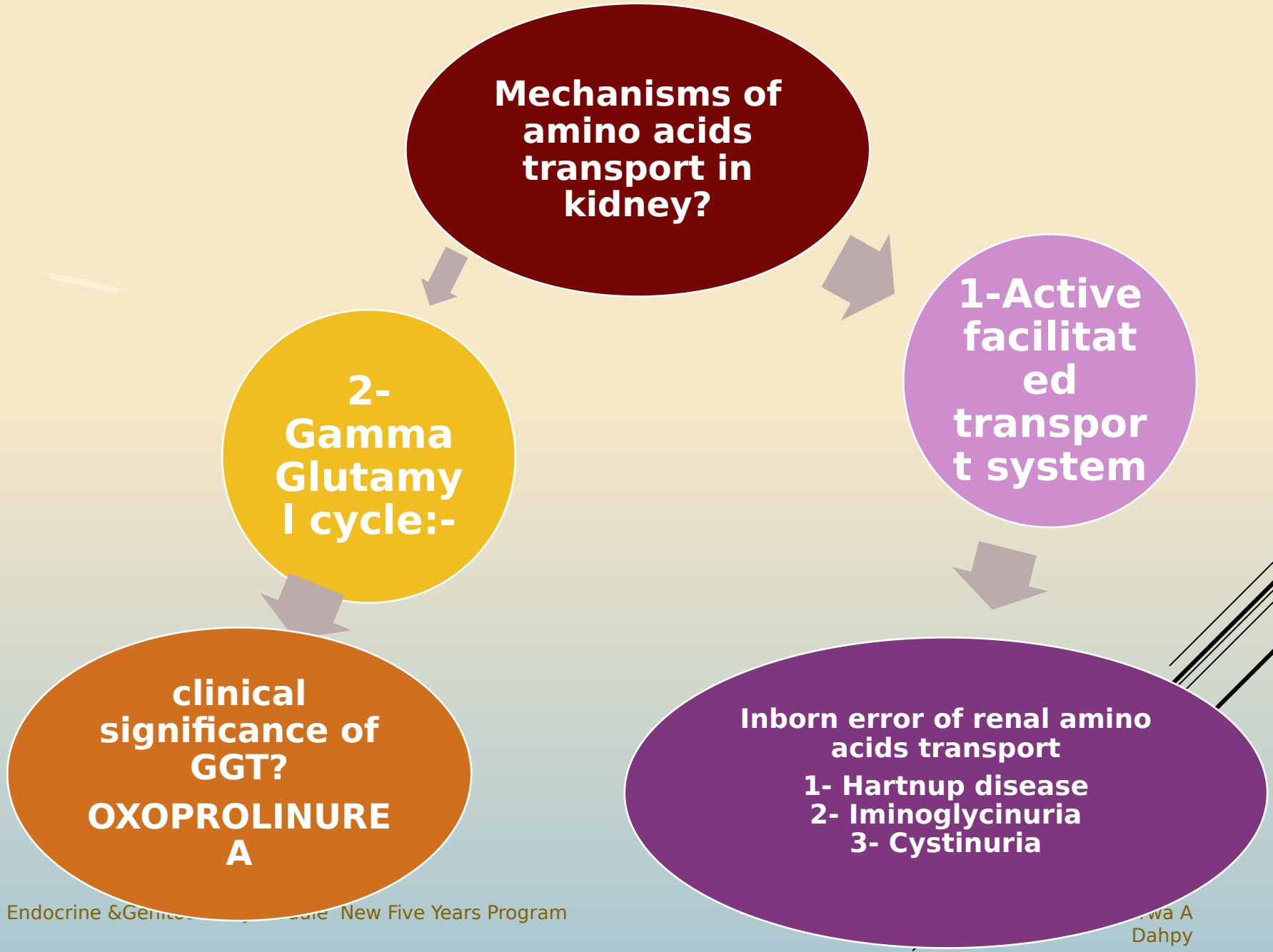
2- Primary hyperoxaluria

Case Scenario



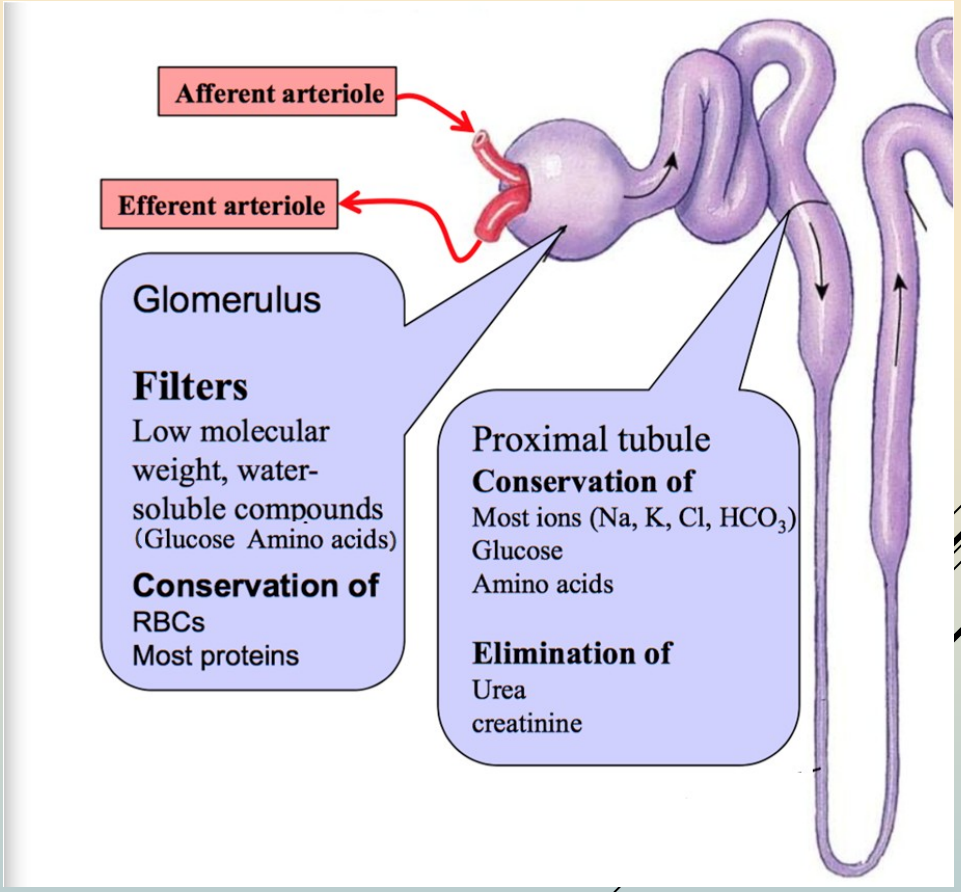
- **Ahmed, a 10 years old boy presented with skin rash, loss of balance (ataxia), mental changes and diarrhea.**
- **His skin rash resembling pellagra**

- The boy did not have the usual dietary deficiency form of pellagra,
- Biochemical findings : large amounts of free amino acids were found in his urine (**neutral aminoaciduria**).
- which indicated a defective **transport of tryptophan** and other **neutral alpha-amino acids** in the small intestine & renal tubules, a disease known as


Mechanisms of amino acids transport in kidney?
1-Active facilitated transport system
2- Gamma Glutamyl cycle:-
clinical significance of GGT?
OXOPROLINURE A
Inborn error of renal amino acids transport
1- Hartnup disease
2- Iminoglycinuria
3- Cystinuria

What is the role of kidney in AA transport (reabsorption)?

- **Amino acids are continuously filtered by the glomeruli & is reabsorbed by the renal tubules**



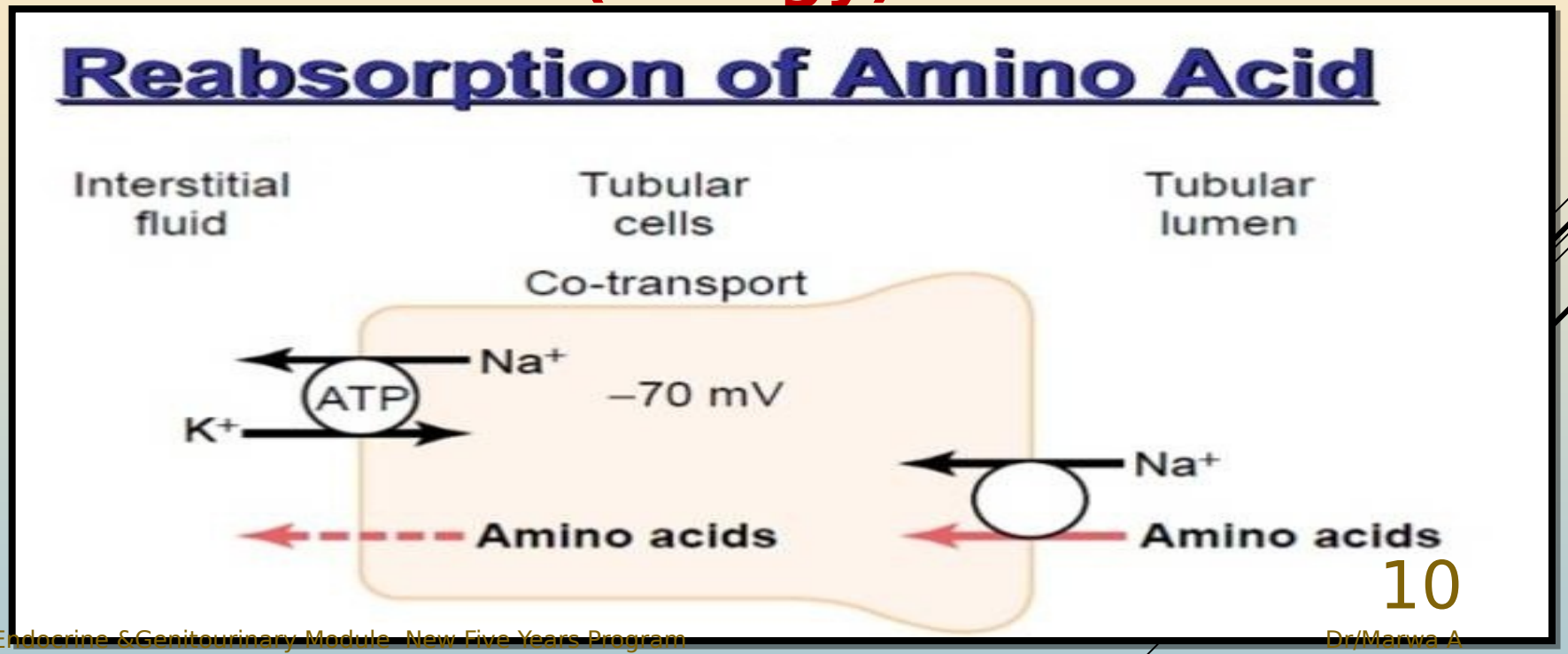
WHAT ARE MECHANISMS OF AMINO ACIDS ?TRANSPORT IN KIDNEY

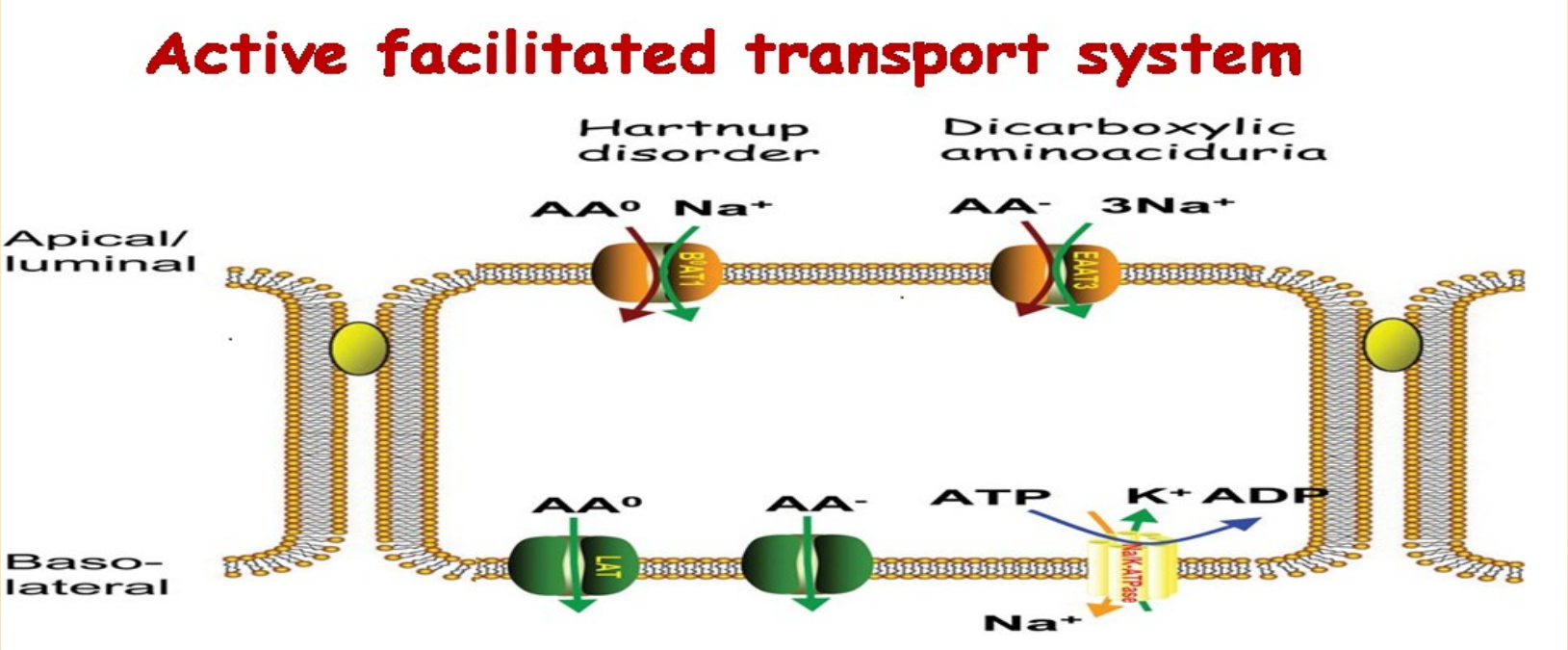
1- Active facilitated transport system

2- Gamma Glutamyl cycle
(Glutathione transport system)

I. Active facilitated transport system??

The Active facilitated transport of L-amino acids require protein carrier & ATP (energy)





-For each group of AAs there is a specific protein carrier

e.g.

- **Small Neutral amino acids**
- **Large Neutral amino acids**
- **Basic amino acids and cystine**
- **Acidic amino acids**
- **Glycine and imino acids.**

Inborn error of renal amino acids transport

1- Hartnup disease

2- Iminoglycinuria

3- Cystinuria

Hartnup disease -1

Hartnup disease (also known as "pellagra-like dermatosis

It is an autosomal recessive metabolic disorder

There is impairment of intestinal absorption and renal reabsorption of neutral amino acids (including tryptophan)

Pellagra like manifestations, aminoaciduria

What is pellagra??

It is a disease that results from nicotinic acid (niacin) deficiency.

Causes:

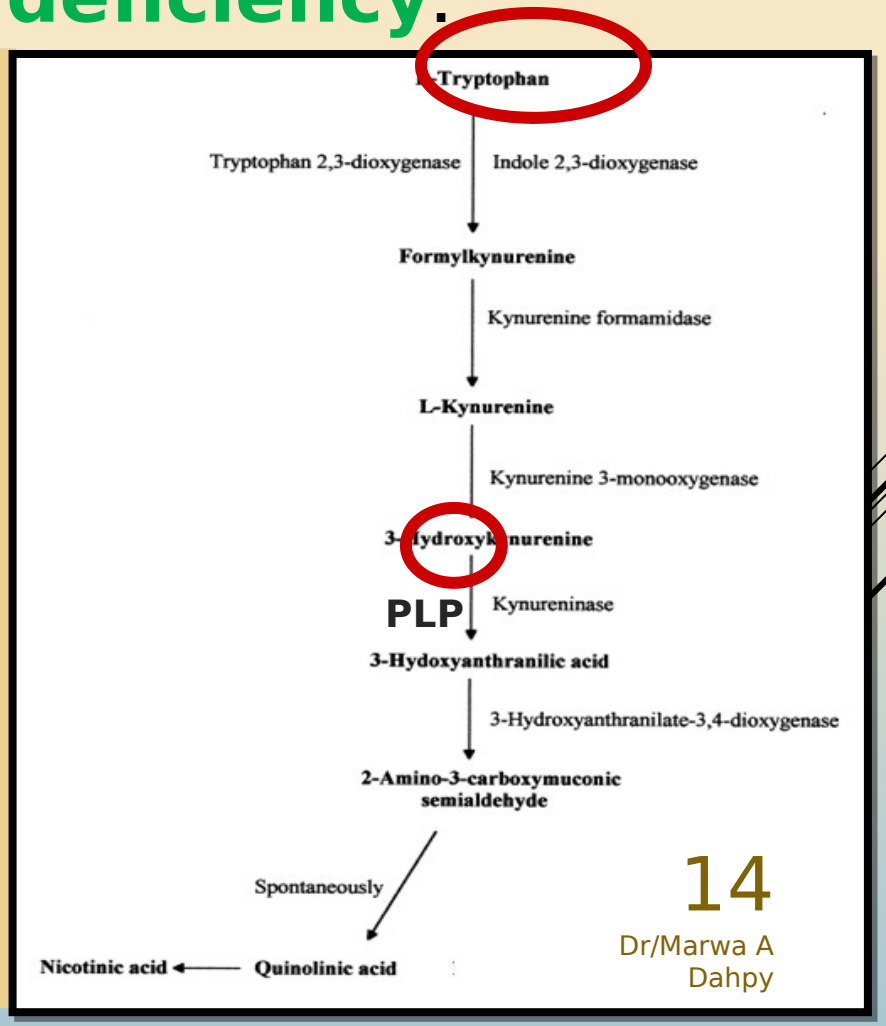
1- Decrease tryptophan in diet. (Zein of maize)

2- Decrease tryptophan absorption (Hartnup disease).

3- Pyridoxal-phosphate deficiency.

4- Carcinoid tumour

(60% of tryptophan is converted into serotonin → ↓ production of nicotinic acid.



- Pellagra symptoms: 4 "D's"
  - Diarrhea
  - Dermatitis
  - Dementia
  - Death

:Treatment

.Treatment of the cause -1

.Nicotinic acid supplement -2

2- Iminoglycinuria

An inherited defect in renal tubular reabsorption of the aminoacid glycine and the imino acids proline and hydroxyproline resulting in excess urinary excretion of all three amino acids.

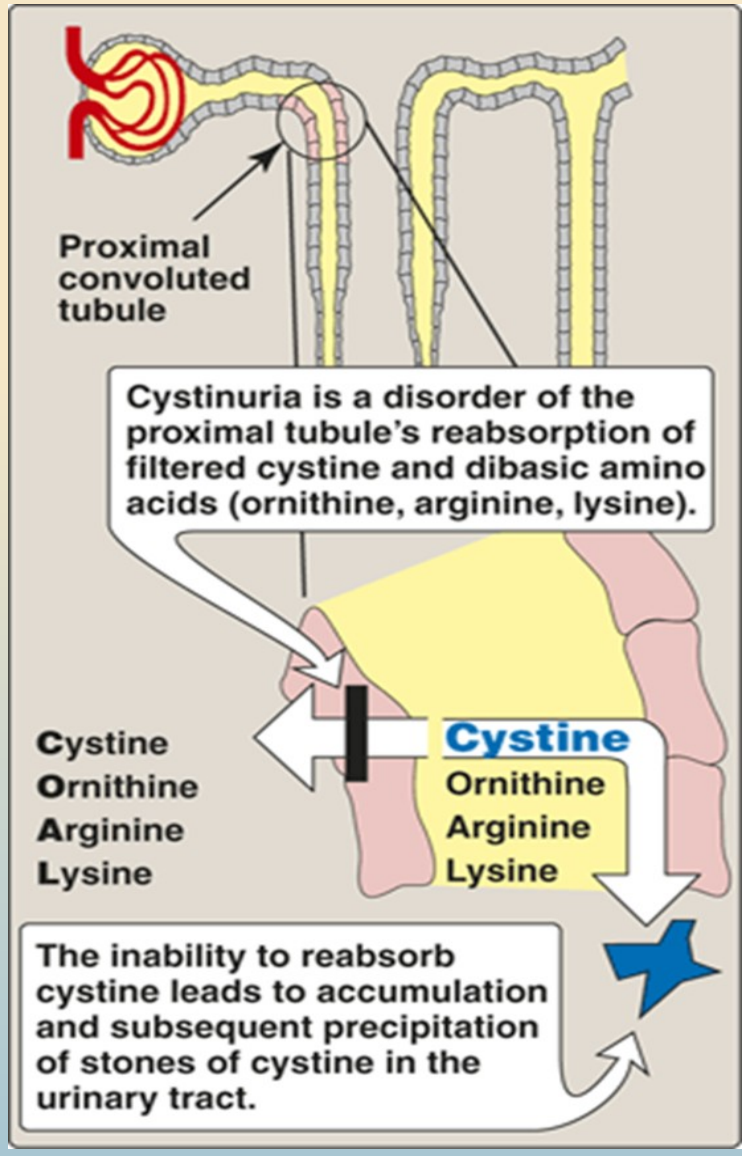
CYSTINURIA -3

An autosomal-recessive defect in the transport protein that is responsible for renal tubular reabsorption of Cystine, Ornithine, arginine and, lysine by renal proximal tubules .

COAL

CYSTINURIA

- It is the most common inborn error of amino acids transport
- About :1 in 7000 births
- The only manifestation of cystinuria is cystine renal stones



PATHOPHYSIOLOGY OF CYSTINURIA

- **Normally** **Amino acids filtered undergo nearly complete reabsorption by proximal tubular cells.**

- **Only 0.4% of the filtered cystine appears in the urine.**

- **There are at least 2 transport systems are responsible for cystine reabsorption:**

High-affinity system

Low-affinity system

PATHOPHYSIOLOGY OF CYSTINURIA

High-affinity system:

- Mediates uptake of **10%** of cystine and the dibasic amino acids at the third segment (**S3**) of the proximal tubule.

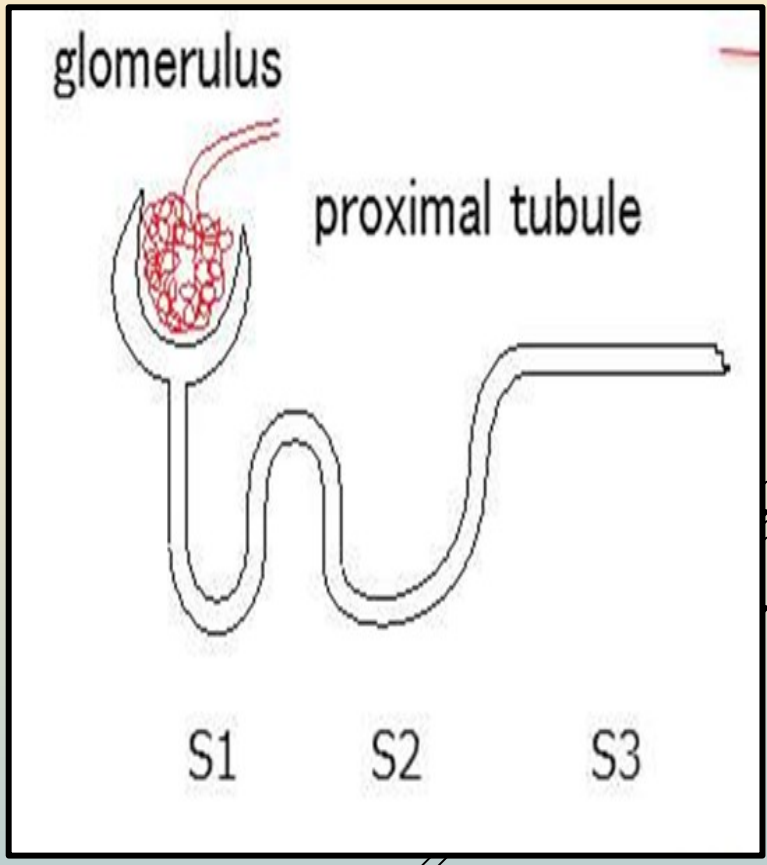
Low-affinity system:

- This system is present in the (**S1-S2**) part of the proximal tubule
- Responsible for **90%** of cystine reabsorption.

- **Affected in**

PATHOPHYSIOLOGY OF CYSTINURIA

- **Defective reabsorption causes elevated levels of dibasic amino acid secretion in the urine.**



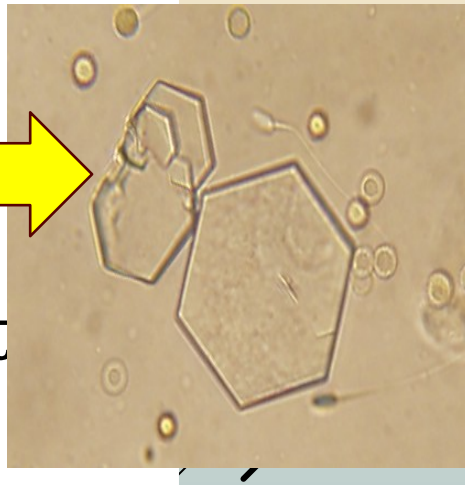
- **Ornithine, lysine, and arginine are completely soluble.**
- **Cystine, which is not very soluble in the urine, forms renal calculi in the acidic**

Cystinuria

- **Symptoms:** Renal colic caused by cystine stones.
- **Diagnosis:** measurement

of cystine excretion in the urine.

- urine analysis: cystine crystals
- **Treatment:** increased fluid int and alkalinization of the urine.



WHAT IS THE SECOND MECHANISM FOR RENAL ?AMINO ACIDS TRANSPORT

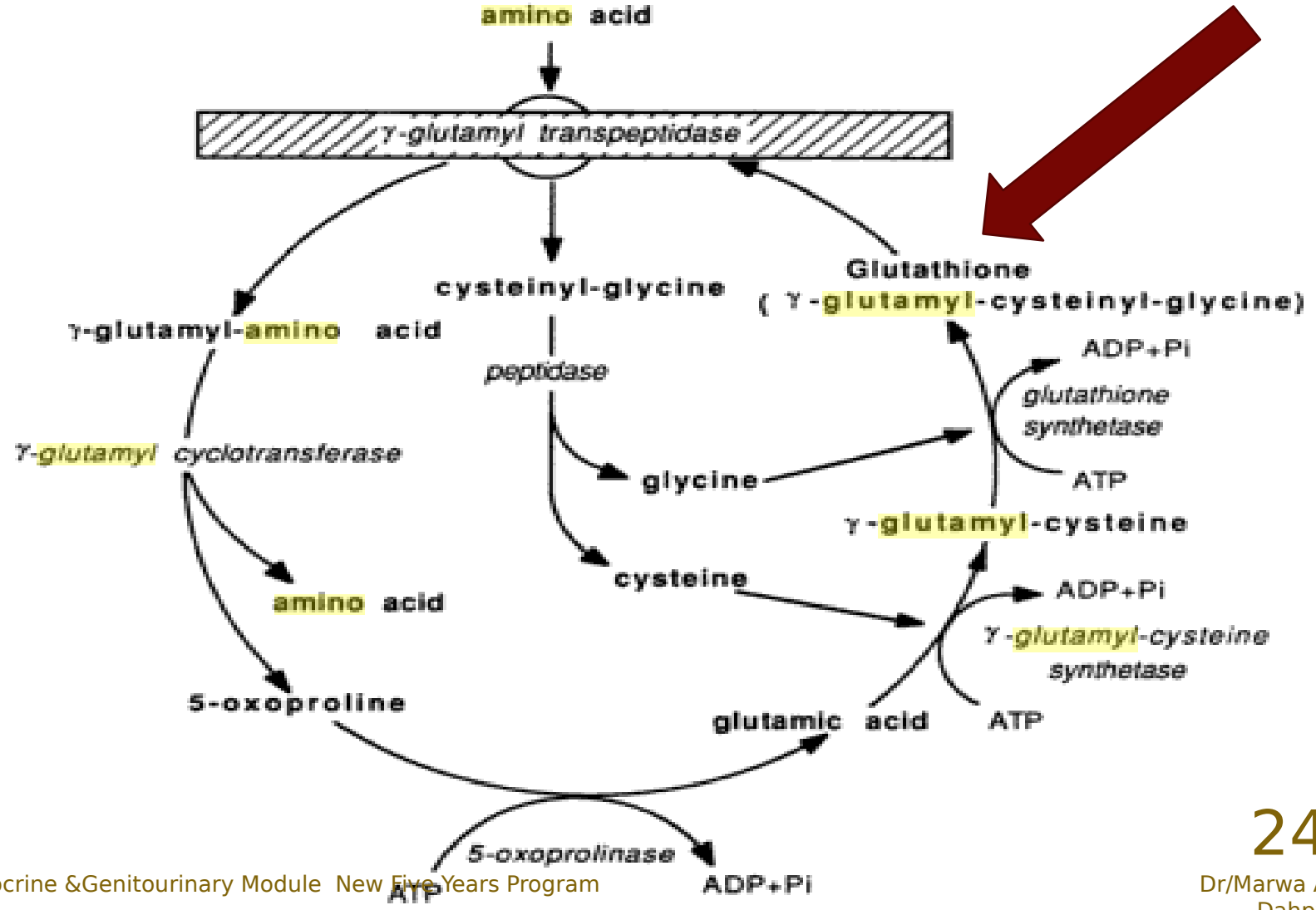
Gamma Glutamyl cycle

(Glutathione transport system)

- **In intestine**
- **Kidney Tubules**
- **Brain**

II- GAMMA GLUTAMYL CYCLE

(GLUTATHIONE TRANSPORT SYSTEM)



γ Glutamyl cycle

Requires 5 enzymes

One is membrane bound

{γ-Glutamyl transpeptidase (GGT)} & 4 are cytosolic

and also needs 3 ATP

?CLINICAL SIGNIFICANCE OF GGT

It is a membrane bound, that is expressed also in the liver and biliary tract cells .

Elevated levels occurs in:

1)Biliary obstruction

2)cancer head of pancreas (pressure on the common bile duct)

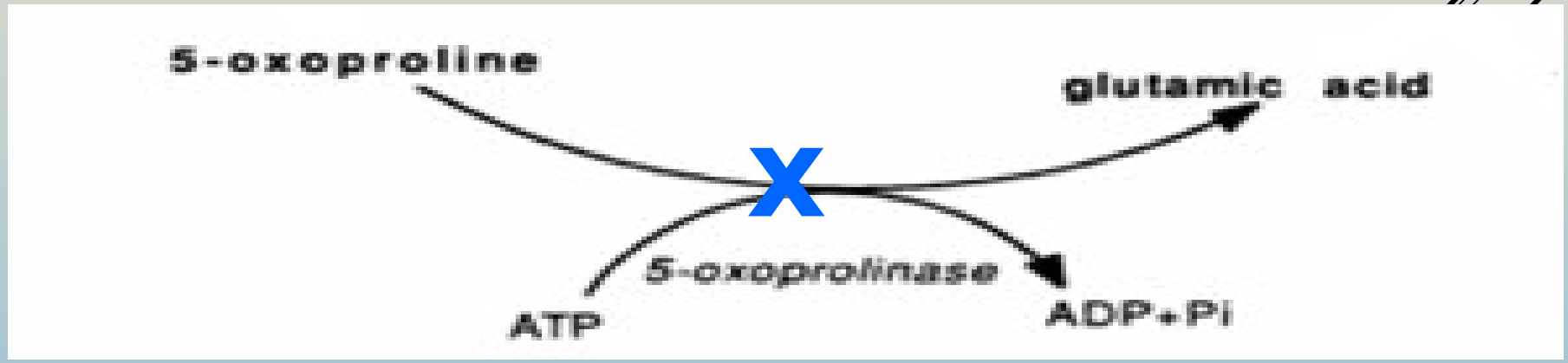
3)Alcoholic liver disease

(the enzyme is induced by alcohol intake).

?WHAT IS OXOPROLINURIA

- **It is a metabolic error caused by a defect in 5-oxyprolinase enzyme**

- **It is characterized by accumulation of 5-oxoproline in blood and hence excreted in urine. It is associated with mental retardation.**



Lecture Quiz

Question 1

Pellagra is due to deficiency of

a) Riboflavin
b) Vitamin C
c) Vitamin D
d) Biotin
e) Nicotinic acid

Lecture Quiz

Question 2

In renal tubule the absorption of amino acid via gamma-glutamyl cycle consume

a) 4 ATP
b) 3 ATP
c) 2 ATP
d) 1 ATP
e) 5 ATP

Metabolic disorders affecting kidney

1- Cystinosis

2- Primary hyperoxaluria

Metabolic disorders affecting kidney

Cystinosis -1

Primary hyperoxaluria -2

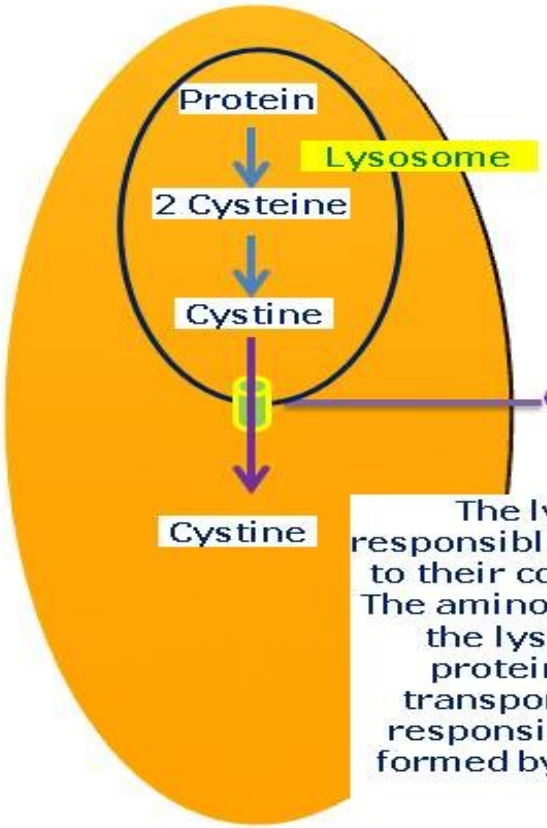

Cystinosis

CYSTINOSIS -1

- **It is a rare disorder caused by a defective carrier that normally transports cystine across the lysosomal membrane from lysosomal vesicles to the cytosol.**

Cystine accumulates in the lysosomes in many tissues and forms crystals & cause tissue damage especially in the kidneys

Cystinosis
Defective gene: CTNS



Cystine crystal

The lysosome in cells is responsible for degrading protei to their constituent amino acids The amino acids then move out the lysosome via transport proteins. Cystinosin is the transport protein specifically responsible for moving cystine formed by combining 2 cysteine amino acids.

Normal Cells

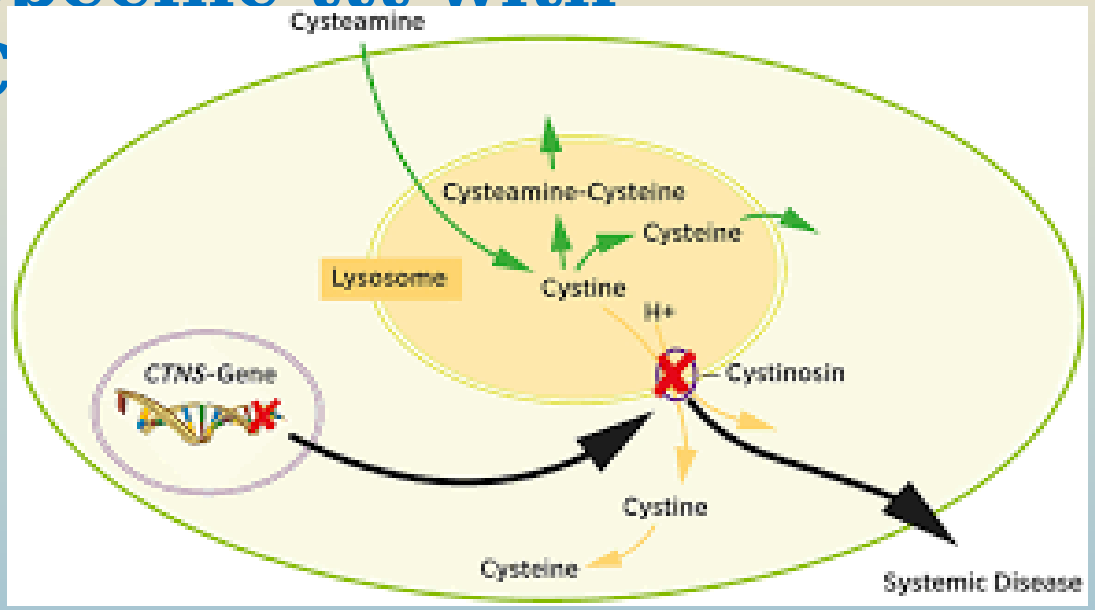
Marc E. Tischler, PhD
Dept of Chemistry & Biochemistry
Univ of Arizona

CLINICAL PICTURE AND TREATMENT OF CYSTINOSIS

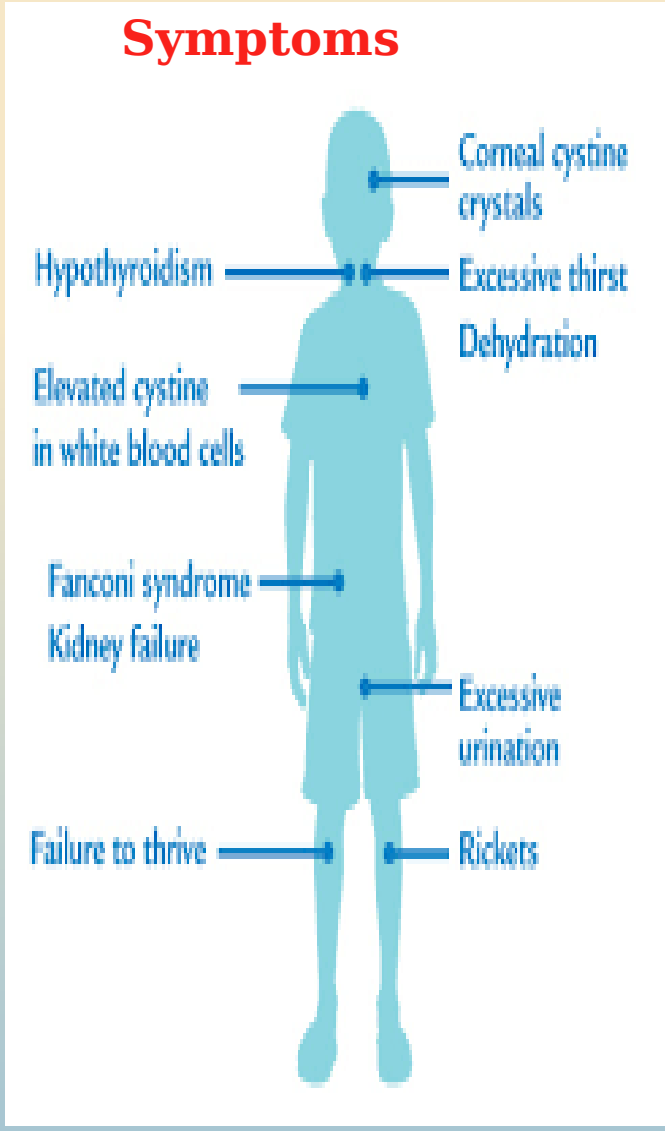
Symptomatic ttt:

- **Free access to water**
- **Replacement of urine loss due to: renal Fanconi syndrome**
- **Hormone replacement when required**

Specific ttt with C



CP and Symptoms



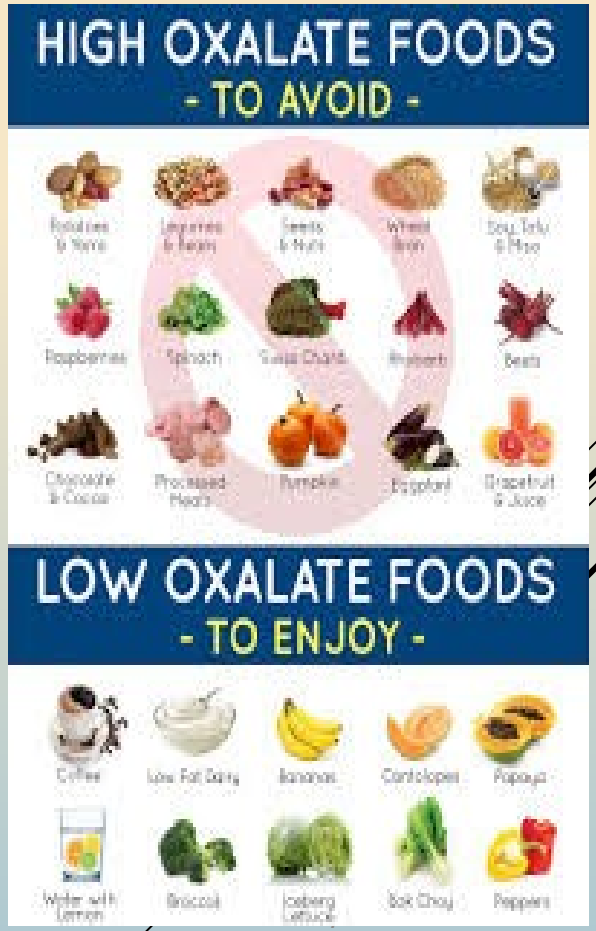
HYPEROXALURIA .2

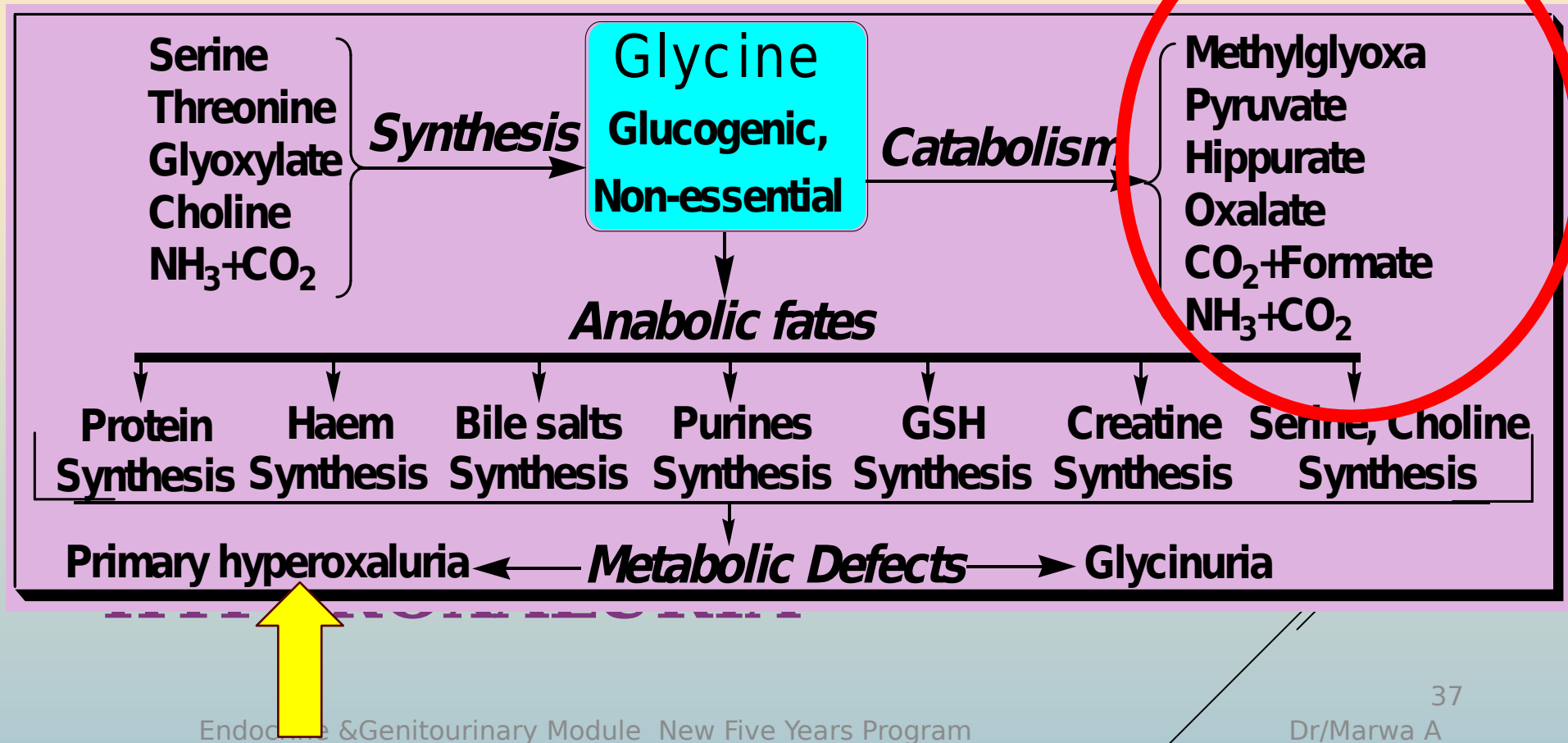
Favors formation of calcium oxalates stones

causes:

1- primary: primary hyperoxaluria.

2- Secondary: increase intake of diet rich in oxalate like chocolate, coffee, tea, Soda, and spinach




Serine
Threonine
Glyoxylate
Choline
NH_3+CO_2
Synthesis
Glycine
Glucogenic,
Non-essential
Catabolism
Methylglyoxa
Pyruvate
Hippurate
Oxalate
CO_2+Formate
NH_3+CO_2
Anabolic fates
Protein Synthesis
Haem Synthesis
Bile salts Synthesis
Purines Synthesis
GSH Synthesis
Creatine Synthesis
Serine, Choline Synthesis
Primary hyperoxaluria
Metabolic Defects
Glycinuria

Primary hyperoxaluria

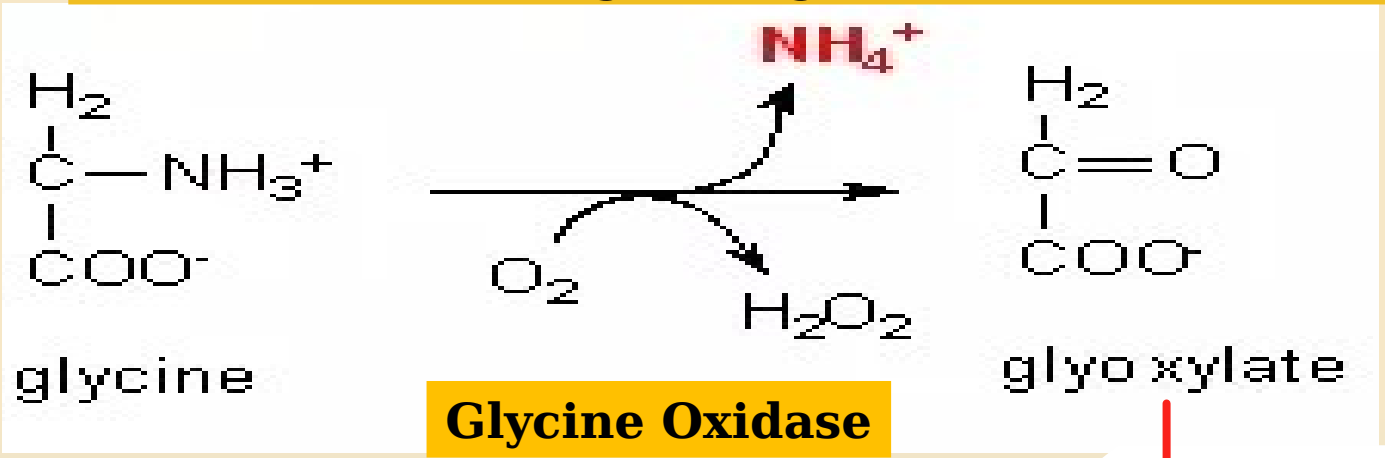
- **Glycine can be deaminated to glyoxylate, which can be:**

Transaminated to glycine by Glycine aminotransferase (alanine: glyoxylate-aminotransferase AGT enzyme) OR

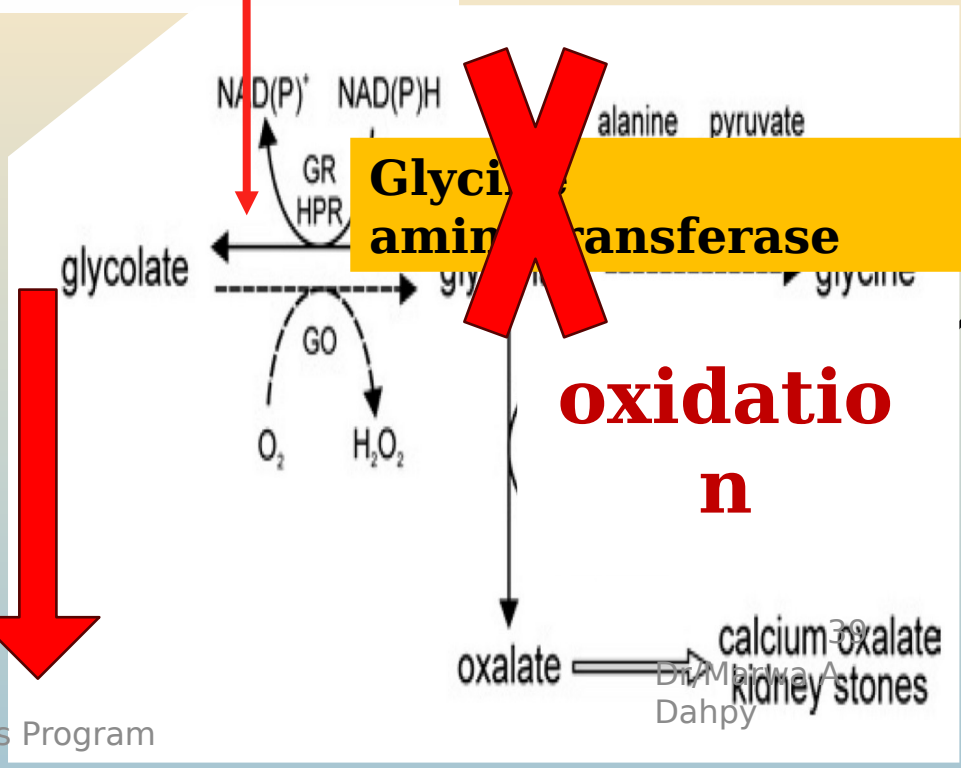
Oxidized to oxalate.

- **Deficiency of the liver peroxisomal enzyme AGT causes overproduction of oxalate, and the formation of calcium oxalate kidney stones (Primary hyperoxaluria)**

Primary hyperoxaluria



Primary hyperoxaluria



Lecture Quiz

Question 3

High excretion of urinary oxalate may due to defect in the metabolism of which of the following

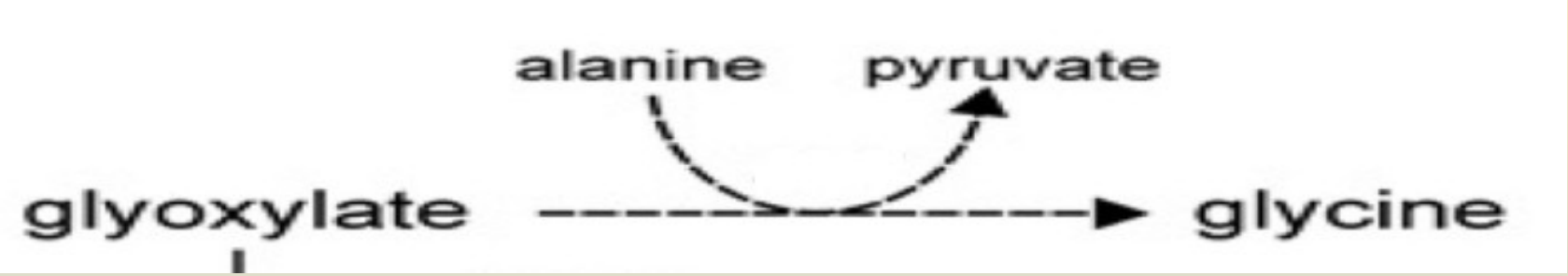
- a. **Glycine**
- **b. Cysteine**
- **c. Nucleic acid**
- **d. Nicotonic acid**
- **e. Hydroxyproline**

Lecture Quiz

Question 4

complete

AGT



SUGGESTED TEXTBOOKS

Lippincott’s Illustrated Reviews- 6th edition.
Harper’s Illustrated Biochemistry-29th edition.

Dr. Marwa Dahpy